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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,199	07/11/2001	Jack R. Wands	21486-032DIV4	1568

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/903,199	Applicant(s) Wands et al
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26, 27, and 39-45* is/are pending in the application.

4a) Of the above, claim(s) *41 and 43-45* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26, 27, 39, 40, and 42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicant's election of species 1, liver cancer. Claims 26, 27 and 39-45 are pending. Claims 41, 43, 44 and 45, drawn to non-elected species, are withdrawn from consideration. It is noted that applicant indicated that claim 43, drawn to cholagiocarcinoma read on the elected species. However, cholangiocarcinoma is a cancer of the bile ducts, which corresponds to a separate species as set forth in Paper No. 8. Claims 26, 27, 39, 40 and 42 are examined on the merits.

2.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

4. The disclosure is objected to because of the following informalities:

(A) The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. The specification contains numerous recitations of HAAH. One species of HAAH is identified in Table 1 as SEQ ID NO:2, encoded by SEQ ID NO:3 (Table 2). The specification refers to other species of HAAH encoded by cDNAs in Table 4 (page 47). When the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Without a sequence identifier, it is unclear if a

reference to HAAH in the specification is synonymous with SEQ ID NO:2. Appropriate correction is required.

(B) Page 6, line 16 contains a blank space after "SEQ ID NO".

Appropriate correction is required.

Claim Objections

5. Claims 26, 27, 40, and 42 are objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Claims 26 recites HAAH. Claim 27 recites "EGF-like repeat sequence". Table 1 identified HAAH as SEQ ID NO:2. The specification identifies SEQ ID NO:4 as the EGF-like repeat sequence. When the claims of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 26, 27, 39, 40 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 are rended vague and indefinite by recitation of "HAAH" and claims 26 and 27 are indefinite in the recitation of "NOTCH" as the only means of identifying the proteins upon which the claimed methods are based. The use of laboratory designations only to identify a particular protein renders the claims indefinite because different laboratories may use the same

laboratory designations to define completely distinct proteins. Amendment of the claims to incorporate a sequence identifier would overcome this rejection.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 26, 27, 39, 40 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are methods which depend upon the identity of the HAAH protein and the NOTCH protein. With respect to the HAAH protein, the instant specification provides a written description of the protein of SEQ ID NO:2 encoded by the cDNA of SEQ ID NO:3. The protein is identified as a human Aspartyl(Asparaginyl) beta Hydroxylase. The specification sets forth SEQ ID NO:2 as HAAH but does not always refer to HAAH as SEQ ID NO:2. When given the broadest reasonable interpretation, the claims drawn to HAAH embody allelic and splice variants as well as fragments of HAAH formed from post-translational cleavage. For example, is known in the art that HAAH undergoes post translational cleavage to produce a smaller protein (Radosevitch, U.S. 6,166,176, column 3, lines 1-10) but there is no written description of the fragment produced thereby. The nature of protein variants produced by allelic sequences, splice variants or post-translational processing is that they are variant structure where the structure and function of one example does not provide guidance to the structure and function of the other members of the genus and the specification provides no teachings to describe any other members

of the genus. According to these facts one of skill in the art would conclude that the applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is therefore insufficient to support the claims to a genus of HAAH proteins.

With regard to the NOTCH polypeptide, the specification does not provide a definition of what constitutes said NOTCH protein but suggests that examples of NOTCH proteins contain the motif of SEQ ID NO:4. However, this embodiment is not present in claims 26, 27, 40 or 42, and is therefore non-limiting to the scope of structures encompassed by claims 26, 27, 40 or 42. When given the broadest reasonable interpretation, the claims drawn to methods which rely on NOTCH proteins embody allelic and splice variants, as well as truncated mutants of NOTCH as well as NOTCH proteins yet to be discovered. Thus the genus is highly variant because numerous structural modifications are permitted. The specification does not disclose a representative number of species which could be indicative of the genus. Further, it is noted that as of the priority date sought, Notch 1 and Notch 2 were characterized in the rat, man and mouse, and Notch 3 was characterized only in the mouse (Lardelli et al, Mechanisms of Development, 1994, Vol. 46, pp. 123-136, page 124, second full pragraph, reference of the IDS filed November, 2001). Thus, the structures encompassed by what was known in the art at the time of filing are not representative of the variant genus of NOTCH proteins. Therefore one of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus as of the priority date sought.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 26, 27 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by DeWys et al (Cancer Chemotherapy Reports, 1973, Vol. 57, pp. 41-49) as evidenced by Hanuske-Abel et al (U.S. 5,789,426) and the Sigma catalog (1997, page 729) and Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference of the IDS filed November 21, 2001) and Kelley et al (Cell, 1987, Vol. 51, pp. 539-548, reference of the IDS filed November 21, 2001). Claim 26 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of a compound which inhibits HAAH hydroxylation of a NOTCH polypeptide. Claim 27 embodies the method of claim 26 wherein said compound inhibits hydroxylation of an EGF-repeat sequences in a NOTCH polypeptide. Claim 39 embodies the method of claim 26 wherein said sequence comprises SEQ ID NO:4 which represents the motif for the EGF repeat sequences.

DeWys et al disclose a method of inhibiting the growth of tumor cells in mice comprising the administration of Mimosine.

Hanuske-Abel et al disclose that human prolyl 4-hydroxylase is inhibited by hydroxypyridone compounds (column 4, lines 7-9. The Sigma catalog identifies L-mimosine as a hydroxy pyridone compound.

Lavaissiere et al disclose that the hydroxylase activities in lung or liver carcinoma cells were substantially higher than hydroxylase activities in corresponding normal cells; and that hydroxylase activity was much higher in hepatic cell carcinoma tissue taken from patients in comparison to adjacent tissue. Lavaissiere et al attribute this increase in hydroxylation activity to the over expression of the HAAH protein (page 1321, first column, first two full paragraphs). Lavaissere et al hypothesize that the EGF-like repeats of the extracellular domain of NOTCH contain the putative consensus sequence fro hydroxylation and that it seems likely that hydroxylation of said repeats regulates the activity of NOTCH proteins (page 1321, second column, first full paragraph). Thus, it is reasonable to conclude that the administration of L-mimosine, which is known to inhibit tumor growth in a mammal (DeWys et al) inherently inhibits

the HAAH hydroxylation of the EGF-repeats in a NOTCH polypeptide. Further, Kelley et al identify the consensus sequence for the EGF repeats in NOTCH which is the same as SEQ ID NO:4 (page 543, Figure 2B, legend, "derived consensus").

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 26, 27, 39, 40, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeWys et al (Cancer Chemotherapy Reports, 1973, Vol. 57, pp. 41-49) as evidenced by Hanuske-Abel et al (U.S. 5,789,426) and the Sigma catalog (1997, page 729) in view of Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference of the IDS filed November 21, 2001) and Kelley et al (Cell, 1987, Vol. 51, pp. 539-548, reference of the IDS filed November 21, 2001). The specific embodiments of claims 26, 27 and

39 are recited above. Claim 40 embodies the method of claim 26 wherein said tumor is liver cancer. Claim 42 embodies the method of claim 26 wherein said tumor is a hepatocellular carcinoma.

DeWys et al teach a method of inhibiting the growth of tumor cells in mice comprising the administration of Mimosine. Hanuske-Abel et al teach that human prolyl 4-hydroxylase is inhibited by hydroxypyridone compounds (column 4, lines 7-9. The Sigma catalog identifies L-mimosine as a hydroxy pyridone compound. DeWys et al do not teach a method of treating liver cancer or hepatocellular carcinoma comprising the administration of L-mimosine of hydroxylpyridone compounds.

Lavaissiere et al teach that the hydroxylase activities in lung or liver carcinoma cells were substantially higher than hydroxylase activities in corresponding normal cells; and that hydroxylase activity was much higher in hepatocellular carcinoma tissue taken from patients in comparison to adjacent non-cancerous tissue. Lavaissiere et al attribute this increase in hydroxylation activity to the over expression of the HAAH protein (page 1321, first column, first two full paragraphs). Lavaissere et al hypothesize that the EGF-like repeats of the extracellular domain of NOTCH contain the putative consensus sequence fro hydroxylation and that it seems likely that hydroxylation of said repeats regulates the activity of NOTCH proteins (page 1321, second column, first full paragraph). Kelley et al identify the consensus sequence for the EGF repeats in NOTCH which is the same as SEQ ID NO:4 (page 543, Figure 2B, legend, "derived consensus"). It is reasonable to conclude that the over expression of HAAH in hepatocellular carcinoma results in the increased hydroxylation of the EGF-repeats of NOTCH proteins as exemplified by the consensus sequence as set forth by Kelley et al.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat hepatocellular carcinoma by the administration of L-mimosine or other hydroxypyridone compounds. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of DeWys on the

toxicity of mimosine against rapidly growing cell systems, the teachings of Hanauske-Abel et al and the sigma Catalog on the inhibition of prolyl hydroxylation by L-mimosine and the teachings of Lavaissiere et al on the elevated level of hydroxylase activity in hepatocellular carcinoma tissues. One of skill in the art would have concluded that the toxicity of L-mimosine against rapidly growing ell systems, such as cancer cells, would be attributed to its inhibition of prolyl hydroxylation, and that L-mimosine would induce a toxic effect on the hepatocellular carcinoma cells due to the inhibition of elevated prolyl hydroxylation caused by the over expression of HAAH.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

February 21, 2003